Table 3. Hydroformylation[a] of isomeric *n*-octenes[b] with **4a**: effect of the ligand:metal ratio.

P:Rh	Yield [%]	TOF [h^{-1}][c]	*n*-Nonanal [%][d]	ROH [%][e]
1:1	66	2270	35.1	2.2
2:1	82	3550	35.2	2.2
5:1	88	5350	35.1	2.2
10:1	93	7390	35.4	1.6

[a] For the procedure see footnote [a] in Table 1. Conditions: $T = 140\,^{\circ}C$; $p = 20$ bar CO/H_2 (1/1); $t = 6$ h. [b] 3.3% 1-octene, 48.4% (*Z*)- and (*E*)-2-octene, 29.2% (*Z*)- and (*E*)-3-octene, 16.4% (*Z*)- and (*E*)-4-octene, 2.1% skeletal octene isomers, 0.6% octane. [c] Turnover frequency at 20% conversion. [d] Fraction of the total amount of aldehydes (four isomers). [e] Total alcohol yield relative to the amount of olefin used. *n*-Octane selectivity: < 1.4%.

Table 4. Hydroformylation[a] of isomeric *n*-octenes[b] with **5**: effect of the ligand:metal ratio.

P:Rh	Yield [%]	TOF [h^{-1}][c]	*n*-Nonanal [%][d]	ROH [%][e]
1:1	21	540	31.7	0.6
5:1	38	1000	41.0	1.4
10:1	52	1320	47.8	1.4
20:1	77	3120	45.9	2.0
50:1	86	2840	47.9	0.8
50:1[f]	73	18710	41.8	0.8

[a]–[e] See footnotes [a]–[e] in Table 3. [f] $[\text{Octene isomers}]_0 = 5.08$ M.

upon use of rhodium catalysts with phosphane ligands that were functionalized with Brønstedt acids.[11, 12] Variation of the active proton group in **5** with respect to donor capability and acidity (SH, COOH, etc.) and the ring size of a potentially hemilabile chelate complex offers potential for further ligand modification.[13]

The results presented here show for the first time that the productivities and selectivities of the technically established high-pressure processes with rhodium catalysts can be achieved with greatly reduced metal concentration and mild reaction conditions (ca. 20–50° lower in temperature and ca. 60–330 bar lower in pressure) and even exceeded with respect to suppression of hydrogenation activity. The introduction of additional oxy groups into monodentate phosphorus ligands ensures at the same time the necessary high isomerization activity of the catalyst and the tendency towards hydroformylation at the chain end. This generally exceeds the optimistic estimates of the potential development of rhodium catalyst for the isomerizing hydroformylation of internal olefins.[4, 10]

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First Noncovalently Bound Calix[4]arene–Gd^{III}–Albumin Complex

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Gadolinium(III) in its chelated form has long-been recognized as being useful as a contrast enhancement agent in magnetic resonance imaging (MRI) because of its f^7 electronic configuration and long relaxation time. Noncovalent attachment of low molecular weight Gd^{III} complexes to serum

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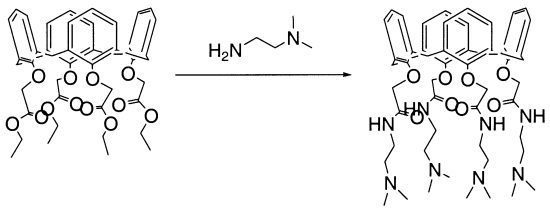
albumin provides macromolecular MR blood pool agents with enhanced efficacy and extended times in the blood-pool without attendant clearance problems.[1] Lauffer et al.[2] and others have reported the synthesis and relaxivity (relaxation rate per mM concentration of Gd^{III}) of noncovalently bound adducts of Gd^{III} complexes.[3] The chelates used have been either diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) derivatives, in which a lipophilic moiety has been attached to the DTPA or DOTA core. Surprisingly, despite all the considerable interest in the development of water-soluble calix[4]arenes capable of binding lanthanide ions for numerous applications,[4, 5] no aqueous solution data are yet available to evaluate their potential as MR contrast agents. Roundhill et al. reported the relaxivity for a calix[4]arene-tetraamide–Gd^{III} complex at 400 MHz.[5] However, their measurement was done in a water/DMSO mixture and therefore is not necessarily valid for biomedical evaluations. Herein, we present the first example of a calix[4]arene–Gd^{III} complex which noncovalently binds to human serum albumin (HSA), as confirmed from its magnetic relaxation dispersion (MRD) profiles.

The novel tetraamidotetraamine compound, 25,26,27,28-tetrakis-*N*-(*N*,*N*-dimethyl-2-aminoethyl)carbamoyloxymethoxycalix[4]arene (**2**) is produced in excellent yield in the single-step reaction of the corresponding tetraethyl ester **1** with *N*,*N*-dimethylethylenediamine at ambient temperature. It is obtained as a white solid and the structure was confirmed



1 **2**

by elemental analysis, ^1H and ^{13}C NMR data, and FAB mass spectrometry. The stability constant for the complexation of Gd^{III} in the cavity formed by the eight oxygen atoms on the lower rim of **2** was found to be $2 \times 10^5\,M^{-1}$ as determined by calorimetric titrations.[6] This number is higher than the previously reported value of $1.0 \times 10^3\,M^{-1}$ for another calix[4]arene–Gd^{III} complex.[5]

The $1/T_1$ and $1/T_2$ MRD data for samples containing 0.001 M $Gd(NO_3)_3 \cdot 5H_2O$ and 0.001 M of tetraamide **2** in the absence and after the addition of 2% or 10% HSA are shown in Figure 1 and Figure 2, respectively. The $1/T_1$ MRD profile of [Gd^{III}(**2**)] is similar to that of the previously reported DTPA–Gd^{III} and DOTA–Gd^{III} complexes.[7] This indicates that the Gd^{III} ion is probably nine-coordinate in solution, with one coordination site occupied by a water molecule. The addition of HSA results in a characteristic peak relaxivity in the MRD profile,[8] which is a result of the increase in the rotational correlation time (tumbling time) of the [Gd^{III}(**2**)] complex caused by its noncovalent interaction with HSA.

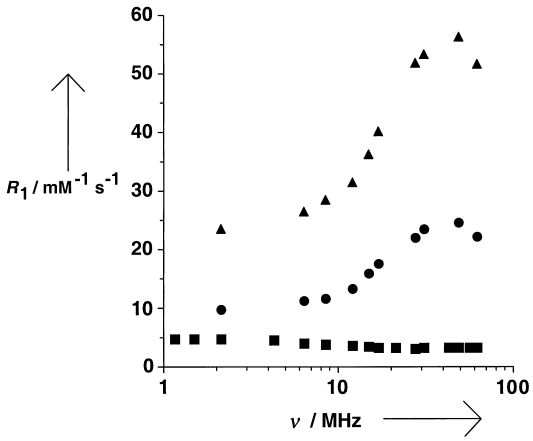


Figure 1. $1/T_1$ ^1H MRD profiles of [Gd^{III}(**2**)] in the absence (■) and in the presence of 2% (●) and of 10% HSA (▲) at 23 °C after subtraction of the HSA contribution. ν = proton Larmor frequency, R_1 = spin–lattice (longitudinal) water proton relaxivity.

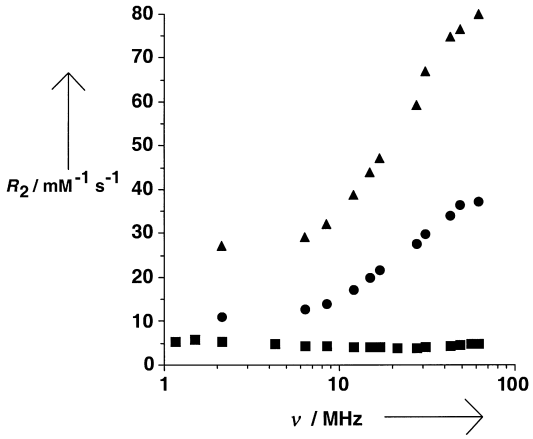


Figure 2. $1/T_2$ ^1H MRD profiles of [Gd^{III}(**2**)] in the absence (■) and in the presence of 2% (●) and 10% HSA (▲) at 23 °C after subtraction of the HSA contribution. ν = proton Larmor frequency, R_2 = spin–spin (transverse) water proton relaxivity.

Upon noncovalent binding to HSA, the Gd^{III} complex behaves as a macromolecule; the binding leads to longer rotational correlation times in solution. Thus, the electron spin relaxation time, which is dependent on the strength of the external magnetic field, dominates and an increase in the relaxivities results with a maximum for [Gd^{III}(**2**)] at a Larmor frequency of about 45 MHz. That the relaxivity for [Gd^{III}(**2**)] in the presence of 10% HSA is higher than in the presence of 2% HSA is due to the additional increase in the rotational correlation time and consequently more pronounced domination of the electron spin relaxation time for [Gd^{III}(**2**)] in the 10% HSA solution. The noncovalent interaction of [Gd^{III}(**2**)] with HSA produces dramatic increases in the $1/T_1$ and $1/T_2$ relaxivities at all field strengths studied compared to those of the unbound complex.

HSA is the most abundant protein in plasma and the noncovalent interaction of [Gd^{III}(**2**)] with HSA in vitro may have strong implications for the future use of calix[4]arene–Gd^{III} complexes in vivo as MR contrast agents. The noncovalent interaction of [Gd^{III}(**2**)] with HSA in vivo would allow its application in dynamic and steady-state MR

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angiography and furthermore indicates the potential to develop a whole new class of MR contrast agents based on water-soluble calixarene chelates.

Experimental Section

The reaction was carried out under argon. The tetraethyl calix[4]arenetetraacetate **1** was prepared according to the literature procedure.[9] The *N*,*N*-dimethylethylenediamine and $Gd(NO_3)_3 \cdot 5H_2O$ were purchased from Aldrich Chemical Co., Milwaukee, WI. Chemical shifts δ are given relative to the relevant standard tetramethylsilane. The stability constant of the [Gd^{III}(**2**)] complex was determined by MicroCal Inc., Northampton, MA.[6]

2: Compound **1** (10.0 g) was added in small portions to *N*,*N*-dimethylethylenediamine (30 mL) and the resulting solution was stirred for 18 h under argon. The unconverted amine was removed by evaporation under reduced pressure and the residue treated with diethyl ether. The white precipitate was filtered, rinsed with diethyl ether, and dried in vacuo. Yield: 11.2 g (92%). m.p. 213 °C. Elemental analysis (%) calcd for $C_{52}H_{72}N_8O_8$: C 66.6, H 7.74, N 12.0; found: C 66.7, H 7.86, N 11.8; FAB-MS: *m*/*z*: 937.5 [M^+]; ^{1}H NMR ($CDCl_3$): $\delta = 2.19$ (s, 24H; NCH_3), 2.44 (t, 8H; NCH_2), 3.22 (d, 4H; CH_2), 3.41 (q, 8H; CH_2NH), 4.44 (s, 8H; CH_2O), 4.47 (d, 4H; CH_2), 6.58 (m, 12H; ArH), 7.57 (br.s, 4H, D_2O exchangable; NH); ^{13}C NMR ($CDCl_3$): $\delta = 31.03$, 37.04, 45.29, 58.11, 74.13, 123.31, 129.02, 134.48, 155.98, 169.76.

MR dispersion measurements: A HSA stock solution (20% w/v) was prepared in deionized water from 96% – 99% albumin (fraction V, Sigma Chemical Co., St. Louis, MO). Relaxation measurements were made on a custom-designed variable field T_1-T_2 analyzer (Southwest Research Institute, San Antonio, TX) at 23 °C. The magnetic field strength was varied from 0.02 to 1.5 T (corresponding to a proton Larmor frequency of 1 – 64 MHz). T_1 was measured by using a saturation recovery pulse sequence with 32 incremental recovery times. The relaxivities (relaxation rates per mM Gd concentration) were obtained after subtracting the water contribution or the appropriate diamagnetic 2% or 10% HSA solution contribution, respectively. T_2 was measured by using a Carr – Purcell – Meiboom – Gill pulse sequence of 500 echoes and a time interval of 2 msec between echos.

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Lithium Amides: Intra-Aggregate Complexation of Lithium and Entropy Control of Basicity

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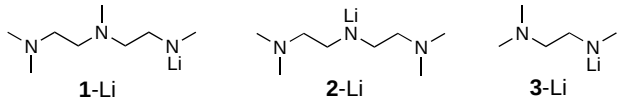
Lithium amides ($LiNR_2$, LiA) are the most widely used reagents for the generation of enolates and their cognate species from carbonyl compounds and related CH acids.[1] This practical importance has led to extensive lists of pK values of secondary amines (HA).[2] However, interpretation of ΔpK values in terms of enthalpy and entropy effects, fundamental to understanding the basicity of lithium amides, is severely limited. Commonly, pK values are determined at a single temperature, usually around 25 °C. This permits only correlation of ΔpK with differences in relative free energy, ΔG_{rel}(LiA(2), LiA(1)), at that temperature.[3] We now report on the prominent influence of entropy on the basicity towards triphenylmethane (TPMH) in THF of lithium *N*-(3,6-diaza-3,6-dimethyl)heptyl-*N*-methylamide (**1**-Li), lithium bis(*N*,*N*-dimethyl-2-aminoethyl)amide (**2**-Li), and lithium *N*-(*N*,*N*-dimethyl-2-aminoethyl)-*N*-methylamide (**3**-Li).[4] Despite the rather special nature of **1**-Li – **3**-Li, our findings have some bearing on the thermodynamics of lithium amides in general.



1-Li and **2**-Li were shown[4] to exist in toluene or THF exclusively as the dimers (**1**-Li)$_2$ and (**2**-Li)$_2$, with exhaustive intra-aggregate complexation of lithium. Their congener **3**-Li lacks one of the amino groups of **1**-Li and **2**-Li and forms an equilibrium mixture (THF, – 108 °C: 2.3:1) of a monomer and a dimer, for which the structures **3**-Li · 2 THF and (**3**-Li)$_2$ · THF were suggested by THF titration,[4] MNDO calculations,[5] and reaction kinetics.[6]

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